Drs. Clarence L. Young and Paul Watkins (liver consultant) reviewed the human liver experience with Factive®. Their key points were:

- in clinical studies, the 320 mg dose appears safe
- lower incidence of hepatobiliary adverse events in gemifloxacin 320 mg (1.5%) vs. trovafloxacin 200 mg (2.8%)
- no evidence for delayed appearance of LFT abnormalities (not affected by duration of exposure)
- available data indicate clinical safety profile comparable to recently marketed fluoroquinolones

Drs. Clarence L. Young, Jean-Paul Ortonne (dermatology consultant), and James Leyden (dermatology consultant) discussed the rash associated with gemifloxacin use. The consultants' key points were:

- consistent with benign, morbilliform rash
- not a predictor for serious dermatological sequelae (e.g., Stevens-Johnson Syndrome or toxic epidermal necrolysis)
- when rash occurred, it was mostly mild to moderate in severity and often resolved spontaneously
- incidence, but not severity, increases with treatment duration

Issues raised by the Agency and discussion follow:

1. In two separate studies (one Phase 1, the other Phase 3), a hepatic signal was associated with the 640-mg gemifloxacin dose. What does this mean?

   Small numbers of subjects in Phase 1 studies (mostly from Dutch centers) received the 640-mg dose. In contrast, when one retrospectively looks at the Trovan NDA, no clear signal (other than the 28-day prostatitis study) was present from the large clinical trial program. SB believes the Agency's concerns can be managed by monitoring post-marketing safety reports, not developing the 640-mg dose further, and stating in labeling that the prescribed dose should not be exceeded.

2. Looking at the amount of gemifloxacin that precipitated in the biliary tract, are patient populations at risk?

   SB would need additional time to address this question.

3. Why are healthy, young women more susceptible to rash?

   SB will look into this further.

4. What should a patient and healthcare provider know about the rash? Should the drug be discontinued immediately upon appearance of a rash? Does Factive sensitize the patients against the quinolone class?

   SB maintains the physician should be contacted if a rash appears. The label will reflect standard statements concerning rash management. Labeling can state that the prescribed duration should not be exceeded.

5. Should additional studies be conducted to address hepatic events or rash?

   Neither SB nor their consultants believe additional safety studies are warranted.

Agency representatives made the following comments:

- In view of the upcoming CDER Pre-decisional meeting to be held November 15, 2000, SB should submit their perspective as to the benefits of gemifloxacin, including a comparison to currently available quinolones/antimicrobials.

- At some point following the CDER Pre-decisional meeting, SB's responses to the Agency's proposed labeling (including microbiologic breakpoints) will be discussed.

- Although SB believes the current MedWatch system is adequate to address the Agency's safety concerns, assuming Factive is approvable, the Agency believes a systematic, structured post-marketing study is warranted.

- The gemifloxacin injection IND is being prepared for a future NDA submission (where more serious treatment indications are being studied). SB should reconsider the viability for their current NDA submission. One option is SB to resubmit the tablet and injection formulations jointly for combined treatment (IV P O transition) of more serious infections. In this situation, the risk/benefit ratio might be more favorable to support approval of the active moiety.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Date of Meeting: August 31, 1999

To: Dr. Edward Yuhas, Associate Director
US Regulatory Affairs
Smith-Kline Beecham
Phone (215) 751-3468
Fax (215) 751-4926

From: Rene Kimzey
Regulatory Project Manager
Phone (301) 827-2196
Fax (301) 827-2326

APPEARS THIS WAY
ON ORIGINAL

IND: —— Factive (gemifloxacin mesylate)

Subject: End-of-Phase-2 Meeting Minutes

h-Kline Beecham Participants:

. Adrian Pritchard
Assistant Director
Safety Assessment, R&D

Dr. Edward Yuhas
Associate Director
US Regulatory Affairs

Dr. John Connelly
Group Director
Safety Assessment, R&D

Dr. Leslie Locke
Associate Director, Anti-Infectives
Clinical R&D and Medical Affairs-US

Dr. Robert Pietrusko
Vice President
US Regulatory Affairs

Julia Bray
nior Statistician
ometrics, R&D

Dr. Clarence Young
Director, Anti-Infectives
Clinical R&D and Medical Affairs-US

Ms. Elizabeth Bygate
Senior Clinical Research Scientist
Clinical Pharmacology, R&D

Dr. Ruth Dixon
Team Leader
Clinical Pharmacology, R&D

Dr. Linda Miller
Assistant Director
Clinical Microbiology

Ms. Ann Allen
Senior Investigator
Clinical Pharmacokinetics, DMPK, R&D

Dr. Vincent Ahonkhai
Vice President, Anti-Infectives
Clinical R&D and Medical Affairs-US

FDA Participants

Dr. John Powers
Medical Officer

Dr. Amy Ellis
Pharmacology/Toxicology Reviewer

Dr. Cheryl Dixon
Statistical Reviewer

Dr. Brad Leissa
Medical Team Leader

Dr. Ken Hastings
Pharmacology Team Leader

Mrs. Rene Kimzey
Regulatory Project Manager

Dr. Dorota Matecka
Chemistry Reviewer

Mr. Peter Dionne
Microbiology Reviewer

Dr. Philip Colangelo
Biopharmaceutics Reviewer

Dr. Mark Goldberger
Division Director, DSPIDP

Dr. Edward Cox
Medical Officer

APPEARS THIS WAY
ON ORIGINAL

The meeting was initiated with a presentation by the sponsor (see attached) covering the following:

- Introduction
- Review of Microbiology Program
- Review of Toxicology Program
- Review of Clinical Program
  - -Phase I Results
  - -Phase III Program
- Summary of Agreements/Conclusions

The remainder of the meeting involved open discussion whose points are summarized below:

The Microbiologist requested that only the organisms related to actual indications be displayed in the data. He also commented that Ciprofloxacin and Ofloxacin were not the best drugs to determine whether *S.pneumoniae* should be classified as quinolone resistant..

The Medical Officer reiterated that the criteria for a definitive diagnosis of *Chlamydia pneumoniae* is a four-fold rise in IgG or IgM titers. A single rise in titers would be classified as presumptive. Since the antibody response to atypical pathogens may be slow, the sponsor is at risk of their not identifying patients with these organisms. The sponsor agreed to the diagnosis criteria and acknowledged the risk involved with cultures.

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ON ORIGINAL

The Microbiologist agreed to the approach that reported results will be from the central laboratory. The sponsor committed to clear notation in the data of any discrepancies between the local and central laboratory results.

A change in the formulation will be considered by the sponsor if thrombophlebitis is seen in the Phase 3 trials. Compatibility with other IV solutions will also be evaluated.

While no effect on blood glucose was seen in earlier studies, the sponsor committed to continued monitoring of glucose, as well as transaminase and liver function.

The Agency encouraged the sponsor to include more seriously ill patients in the nosocomial pneumonia study, and to include optional aminoglycosides or glycopeptides where clinically indicated. Comparators such as cefepime or imipenem were suggested. The Agency expressed concern that the currently planned study may not be generalizable to the general population.

A more in-depth definition of the ATS guidelines will be included in the study by the sponsor.

The use of comparators approved for the indication sought was suggested by the Agency.

The Agency recommended powering a delta of 10% for each indication. If this delta was exceeded, input from the Advisory Committee may be sought.

The Pharmacologist agreed that the sponsor's plan for conducting non-clinical studies to support the IV product appeared reasonable.

The meeting was concluded with a summary of the discussion.

Please feel free to contact me at the above numbers for any questions or concerns.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Rockville, MD 20857

Meeting Date: May 27, 1999

To:
Edward M. Yuhas, Ph.D
Associate Director, U.S. Regulatory Affairs
SmithKline Beecham
Phone (215) 751-3886
Fax (215) 751-4926

APPEARS THIS WAY
ON ORIGINAL

From:
Rene Kimzey
Project Manager, DSPIDP
Phone (301) 827-2196
Fax (301) 827-2326

Subject: Pre-NDA Meeting

IND: [redacted]

FDA Attendees:

Sandra Kweder, M.D., Acting Director ODE IV
Mark Goldberger, M.D., M.P.H., Director, DSPIDP
Brad Leissa, M.D., Medical Team Leader, DSPIDP
John Powers, M.D., Medical Officer, DSPIDP
Norman Schmuff, Ph.D., Chemistry Team Leader, DSPIDP
Dorota Matecka, Ph.D., Chemistry Reviewer, DSPIDP
Amy Ellis, Ph.D., Pharmacology/Toxicology Reviewer, DSPIDP
Peter Dionne, M.S., Microbiology Reviewer, DSPIDP
Philip Colangelo, Ph.D., Biopharmaceutics Reviewer, DSPIDP
Nancy Silliman, Ph.D., Statistical Team Leader, DB III
Cheryl Dixon, Ph.D., Statistical Reviewer, DB III
Rene Kimzey, RNC, M.Ed., Project Manager, DSPIDP

SmithKline Beecham Attendees:

Duncan McKay, Director Anti-infectives, Clinical R&D and Medical Affairs-Europe
Robert Pietrusko, Ph.D., Vice President, U.S. Regulatory Affairs
James Poupard, Ph.D., Director Antimicrobial Profiling & Clinical Microbiology

John Wojcik, Asst. Director, Electronic Submissions Group, Regulatory Affairs
Clarence Young, M.D., Director, Anti-Infectives Clinical R&D and Medical Affairs -U.S.
Sheila Young, Senior Clinical Scientist,Clinical R&D and Medical Affairs-U.S.
Edward Yuhas, Ph.D., Associate Director, U.S. Regulatory Affairs
Jane Finlay, Senior Scientist, Antimicrobial Profiling & Clinical Microbiology
Michael Brennan, Ph.D.,Director Electronic Submission Group
John Davies, Senior Statistician, Biometrics
Daniel Burch, Ph.D., Group Director, Anti-infectives, ClinicalR&D and Medical Affairs
Vincent Ahonkhal, M.D., Vice President, Clinical R&D and Medical Affairs-U.S.
Deborah Hepworth, Principal Statistician, Biometrics, R&D

The sponsor opened the program with a slide presentation (attached) covering the following items:

- Introduction
- General NDA Organization
- Overview of Clinical Development Program
- Review of ISE Organization
- Review of ISS Organization
- Review of Microbiology Organization
- Discussion of Electronic Components of Submission

Discussion of the above items and related issues were as follows:

The general NDA organization proposed by the sponsor appeared acceptable, although many specifics are yet to be presented to the Agency. A future meeting among the chemists will be arranged to talk about CMC.

Negotiations about the name Factive can be arranged by Dr. Dan Boring of the LNC. Possibilities include a meeting/teleconference facilitated by Dr. Boring between the two companies with similar name requests or simply the selection of an alternate name by one or both parties.

The Agency requested that the label clearly state dosing regimens by indication and that the specific organisms be listed by genus and species.

The Medical Officer stated the criteria for a definitive diagnosis of *chlamydia pneumoniae* is a four-fold rise in IgG or IgM titres.

The sponsor needs to define the parameters of abnormal liver function tests in the submission, as well as indicating whether this is a change from baseline. Hepatic Adverse Events should address hepatitis, hyperbilirubinemia, and elevated transaminase.

It was requested that SKB classify patients as success or failure, not unable to determine. How patients "lost to follow-up" appear in the data also needs clarification. The ISE data shows patients as a percent of success. The Agency would also like the actual number in each category to be listed.

The following conditions must be met to obtain the specific indication of ——

The Agency felt the separation of the data from the U.S./Canada and Mexico studies would be desirable. The sponsor responded that the numbers from Mexico were very small, and they would prefer to show them separately only if there was a radical difference. The Agency agreed to this approach.

SKB requested Agency concurrence to use study 003 as a pivotal study for the ——, indication. The Agency stated that it could be used as a supporting study when adjusted for multiple comparisons and if the primary —— margin.

Retaining the —— approach as the primary analysis of protocol 053 and additionally presenting the results with a —— adjustment was deemed acceptable to FDA.

The sponsor was advised to consider the —— issue which FDA's European counterparts are currently scrutinizing.

The sponsor indicated an interest in doing pediatric studies in the future, but would not be including them in the initial NDA submission.

The acceptability of an unapproved comparator will be reviewed when more specifics are available to the Agency.

APPEARS THIS WAY
ON ORIGINAL

ERS Comments:

- Both ISE and per protocol to be in text format
- If CRF's are already scanned in, please provide all CFR's, but if not, FDA reviewers would plant to request a random sample
- References should be provided in a paper format
- Secure E-mail would be helpful

Please feel free to contact me at the above numbers for any questions or concerns.

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ON ORIGINAL

4 Pages have been redacted in full from this document

Reason:

_____ b(2) 'low'
__X__ b(4) CCI
_____ b(4) TS
_____ b(5) Deliberative Process: Attorney Client and Attorney Work Product Privilege
_____ b(6) Personal Privacy
_____ b(7) Law Enforcement Records

[Federal Register: February 12, 2003 (Volume 68, Number 29)]
[Notices]
[Page 7126-7127]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr12fe03-48]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

APPEARS THIS WAY ON ORIGINAL

Anti-Infective Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). At least one portion of the meeting will be closed to the public.

Name of Committee: Anti-Infective Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on March 4, 2003, from 8 a.m. to 5 p.m., and March 5, 2003, from 9 a.m. to 5 p.m., and March 6, 2003, from 8 a.m. to 12 noon.

Location: Marriott Washingtonian Center, Grand Ballroom, 9751 Washingtonian Blvd., Gaithersburg, MD.

Contact Person: Tara P. Turner, Center for Drug Evaluation and Research (HFD-21), Food and Drug Administration, 5600 Fishers Lane (for express delivery, 5630 Fishers Lane, rm. 1093), Rockville, MD 20857, 301-827-7001, e-mail: TurnerT@cder.fda.gov, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12530. Please call the Information Line for up-to-date information on this meeting.

Agenda: On March 4, 2003, the committee will discuss new drug application (NDA) 21-158, Factiver (gemifloxacin mesylate) Tablets, Parexel International, U.S. Agent for LG Life Sciences, Ltd., proposed for the treatment of Community-Acquired Pneumonia (CAP) and Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB). On March 5, 2003, the committee will discuss the formation of a list of pathogens of public health importance for which antimicrobial drug development would be desirable. The committee also will discuss the concept of how preclinical data and clinical data from one disease state may support approval of antimicrobial drugs in another, separate disease state.

Procedure: On March 4 and 5, 2003, the meeting is open to the public. Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written

submissions may be made to the contact person by February 25, 2003. Oral presentations from the public will be scheduled between approximately 1 p.m. and 1:30 p.m. on both days. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before February 25, 2003, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Closed Committee Deliberations: On March 6, 2003, from 8 a.m. to 12 noon, the meeting will be closed to permit discussion and review of trade secret and/or confidential information (5 U.S.C. 552b(c)(4)).

Persons attending FDA's advisory committee meetings are advised that the agency is not responsible for providing access to electrical outlets.

FDA welcomes the attendance of the public at its advisory committee meetings and will make every effort to accommodate persons with physical disabilities or special needs. If you require special accommodations due to

[[Page 7127]]

a disability, please contact Tara Turner at least 7 days in advance of the meeting.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: February 3, 2002.
Linda Arey Skladany,
Associate Commissioner for External Relations.
[FR Doc. 03-3437 Filed 2-11-03; 8:45 am]

BILLING CODE 4160-01-S

Medical Team Leader's and Division Director's Review
NDA 21-158

Factive® (gemifloxacin mesylate) for Community Acquired Pneumonia and Acute Exacerbation of Chronic Bronchitis

Date: April 4, 2003

From: Edward M. Cox, M.D., M.P.H.,
Medical Team Leader (MTL), DSPIDP, HFD-590

Renata Albrecht, M.D.
Director, DSPIDP, HFD-590

Through: Mark Goldberger, M.D., M.P.H.
Director, ODE IV, HFD-104

APPEARS THIS WAY
ON ORIGINAL

Re: Factive® (gemifloxacin mesylate) Tablets
Parexel International, U.S. Agent for LG Life Sciences, Ltd.

APPEARS THIS WAY
ON ORIGINAL

Original Submission Date: December 15, 1999
First Action Letter Date: December 15, 2000
First Action: Not Approvable

Resubmission Date: October 4, 2002
Action Date: April 4, 2003

MTL's / Director's Recommended Regulatory Action:

Approval for Factive (gemifloxacin) for mild to moderate community acquired pneumonia and acute bacterial exacerbation of chronic bronchitis (see end of document for details.)

Background

The original NDA for Factive (gemifloxacin) Tablets was submitted on December 15, 1999 by Smith Kline Beecham (later GlaxoSmithKline). In the original NDA submission the Applicant sought claims for the treatment of adults for the following indications

- Community-acquired pneumonia (CAP) 320 mg [redacted]
- Acute bacterial exacerbation of chronic bronchitis (ABECB) 320 mg [redacted] days

APPEARS THIS WAY
ON ORIGINAL

The efficacy of gemifloxacin, in general, in 4 of the originally proposed five indications (CAP, —— ABECB, ——, was found to be non-inferior to the comparator regimens; no convincing evidence of clinical superiority to comparators or of unique clinical advantage was identified in the studies submitted. The question of added benefit arose because during the course of the NDA review significant questions arose regarding the safety of gemifloxacin. These questions centered around the higher than expected rate of rash reported in patients receiving gemifloxacin, notably women and patients under the age of 40 years, and related questions regarding the mechanism of the observed rash, the potential for cross-sensitization, and the possibility that the frequent occurrence of rash may portend a risk for more serious infrequent cutaneous drug reactions. In addition, there were also unresolved questions regarding the hepatic safety profile of gemifloxacin, and observation of infrequent, dose-dependent increases in ALT, AST, alkaline phosphatase and bilirubin. In clinical pharmacology studies, a modest prolongation in QT similar to that seen with other quinolones was noted.

The OPDRA safety meeting was held November 6, 2000, a meeting took place with GSK November 7, 2000, and a Pre-Decisional Meeting (now Regulatory Briefing) was held November 15, 2000. Based on input from these meetings, GSK was issued a Not Approvable letter December 15, 2000 which presented detailed descriptions of the deficiencies and asked GSK to further address the adverse reactions, notably rash, liver toxicity and QT prolongation.

GSK submitted administrative NDA ——

GlaxoSmithKline initiated study 344, designed in consultation with FDA, to address the incidence of rash and related questions. During the development of this protocol, GSK met with the agency on February 22, 2001 to reach agreement on issues related to the design of study 344. The trial enrolled 1,011 women under the age of 40, because these patients were most likely to provide important safety information (see study description and results below). The applicant also conducted

2 additional CAP studies to gain additional information on PRSP and the 7-day treatment regimen, and 5 additional ABECB studies; the latter evaluated the efficacy of gemifloxacin in treatment and had further follow-up to examine the duration of relapse free post treatment interval.

The applicant requested a pre-resubmission meeting with FDA; this took place on February 27, 2002. During the meeting, the company presented an update on the efficacy of the product, including results of CAP studies and data on ——— They also presented results of their analysis of study 334 which showed an incidence of rash in 31.7% (260/819) gemifloxacin treated women compared to 4.3% (7/164) in ciprofloxacin treated women (gemifloxacin 320 mg po qd for 10 days vs. —— ciprofloxacin 500 mg po bid for 10 days). Following an in-depth discussion, the agency informed the applicant that the risk of rash may be reasonable for indications such as CAP and ABECB and it is possible these indications could achieve a satisfactory risk benefit profile. The agency further added that approval of ——— given the incidence of rash, would most likely be difficult and finally that there were serious concerns about the risk/benefit for ——given that this infections is seen essentially in young women, the population that also appears to have the highest incidence of rash after gemifloxacin.

GSK subsequently transferred gemifloxacin back to LG Life Sciences, Ltd. of Korea; PAREXEL International was retained as agent to LG Life Sciences, Ltd. along with GeneSoft Pharmaceuticals. LG Life Sciences resubmitted NDA 21-158 on October 4, 2002 and is currently requesting only the indications of CAP and ABECB in adults, having re-visited the proposed indications and taking into consideration the higher rate of rash with gemifloxacin (especially in women and younger adults) and the increased frequency of rash as duration of treatment increases. The re-submission contained the data from study 344 on rash, information on the microbiologic activity of gemifloxacin, and additional clinical data from studies of CAP and ABECB. The additional CAP data and re-analyses of existing CAP data provide some information on the severity of disease in patients from the CAP clinical studies and treatment of CAP due to resistant *S. pneumoniae*.

The drug was studied under ————originally submitted August 6, 1997. An intravenous formulation IND was submitted April 6, 2000 but development of this formulation has been delayed. The product was submitted to other regulatory agencies and is currently approved in New Zealand and Korea, but is not currently marketed.

Microbiologic Data

Gemifloxicin exhibits *in vitro* microbiologic activity against a number of gram-negative and gram-positive organisms. While gemifloxacin has lower MIC values for gram-positive organisms than many other flouroquinolones, the AUC and C_{max} values attained with the proposed dosing regimen of 320 mg po qd, is lower than for other fluoroquinolones, and largely offsets the MIC value advantage. In studies done

primarily with *Streptococcus pneumoniae*, gemifloxacin inhibits DNA synthesis by inhibiting both DNA gyrase and topoisomerase IV at therapeutically relevant levels.

The company provided data from in vitro analyses and animal models of infection evaluating the activity of gemifloxacin against strains of *S. pneumoniae* with mutations in the DNA gyrase or the topoisomerase IV or both genes. For some of the strains tested, gemifloxacin MICs remained within the susceptible range (based on in vitro testing) in the presence of some of these mutations; this was not necessarily true for some of the other flouroquinolones tested. However, based upon the clinical data, there was only very limited clinical experience with S. *pneumoniae* strains with MIC values in excess of 0.06 µg/mL. Therefore a breakpoint of 0.12 µg/mL was recommended for *S. pneumoniae*.

Community Acquired Pneumonia (CAP)

The Applicant's proposed indication for CAP includes claims for penicillin-, clarithromycin- and cefuroxime-resistant strains of *Streptococcus pneumoniae*, and initially included all degrees of severity but was subsequently modified to limit the indication to mild-to-moderate severity:

> **Community-acquired pneumonia** (of mild to moderate severity) caused by *Streptococcus pneumoniae* (including penicillin-resistant, macrolide-, cefuroxime-resistant, and ciprofloxacin non-susceptible strains), *Haemophilus influenzae; Haemophilus parainfluenzae; Moraxella catarrhalis;-Mycoplasma pneumoniae; Chlamydia pneumoniae; Legionella pneumophila; Klebsiella pneumoniae; Staphylococcus aureus.*

The proposed dose and duration is gemifloxacin 320 mg po qd for 7 days.

The clinical data in support of the proposed CAP indication were derived from a total of 6 studies. Four of the studies were controlled studies, three of which were double-blind randomized studies. There were also 2 additional uncontrolled studies (Table 1).

Table 1. Community Acquired Pneumonia: Controlled and Uncontrolled Studies of Gemifloxacin

Study	Treatment Regimen	Duration	N*	Geographic Region
Controlled studies				
011	gemifloxacin 320 mg po qd	7 days	168	Europe, S. Africa
	amoxicillin /clavulanate po 1g/125 mg tid	10 days	156	
012	gemifloxacin 320 mg po qd	7 or 14 days	319	U.S. Canada, Europe, S. Africa
	cefuroxime 500 mg po bid /clarithromycin 500 mg po bid	7 or 14 days	322	
049	gemifloxacin 320 mg po qd	7 or 14 days	290	U.S., Mexico, Spain
	trovafloxacin 200 mg po qd	7 or 14 days	281	
185	gemifloxacin 320 mg po qd	7-14 days	172	Australia, Europe, Philippines Guatemala, Lebanon, Singapore, and North America
	ceftriaxone 2g IV qd → cefuroxime 500 mg po bid**	1-7 days + 1-13 days (IV/oral= ≤14)	173	
Uncontrolled studies				
061	gemifloxacin 320 mg po qd	7 days	216§	World-Wide (Except N. America)
287	gemifloxacin 320 mg po qd	7 days	188	Asia, U.S., Mexico Philippines

* N refers to the number of randomized patients (enrolled for uncontrolled studies)
§ Study 061 was conducted in patients with CAP or ABECB. Only data from the 216 patients with CAP are included in this table and the discussion herein regarding CAP.

The patients enrolled in the CAP studies had a mean age of approximately 55 years of age. The racial distributions in the study populations were approximately 80% white, with smaller percentages of Black, Oriental, and other race categories. The Applicant's results from the controlled CAP studies support that gemifloxacin is non-inferior to its comparators (Table 2).

Table 2. Summary of Clinical Response at Follow-Up in the Clinical Per Protocol Population: CAP Controlled and Uncontrolled Studies 011, 012, 049, 185, 061 and 287

	Success Rate		Treatment Difference
	Gemifloxacin % (n/N)	Comparator* % (n/N)	% (95% CI)**
Controlled Studies			
Study 011	88.7% (102/115)	87.6% (99/113)	1.1 (-7.3, 9.5)
Study 012	87.6% (220/251)	92.6% (238/257)	-5.0 (-10.1, 0.2)
Study 049	94.0% (202/215)	89.9% (186/207)	4.1 (-1.1, 9.3)
Study 185	92.2% (107/116)	93.4% (113/121)	-1.15 (-7.73, 5.43)
Uncontrolled Studies			
Study 061	91.7% (154/168)	-	(86.1, 95.2)
Study 287	89.8% (132/147)	-	(84.9, 94.7)

Three of the four controlled CAP studies used a gemifloxacin regimen of '——— days" or '——————— From the analyses of gemifloxacin associated rash, longer duration of therapy is associated with an increasing rate of rash (Figure 1). Also, the trend in drug development is toward shorter duration regimens in the treatment of bacterial respiratory infections. Therefore, the Applicant is asking for a regimen for therapy of CAP of only 7 days duration ———————

The results of the Agency's analysis of data based on the actual duration of therapy is presented in Table 3. The decision of whether to treat for ——— in studies 12, 49 and 185 was made when the patient was already on therapy (approximately day 2-4); patients were not randomized to either ——— on entry. Study medication could be extended to 14 days if the patient had a severe infection, if the pneumonia was confirmed or suspected to be due to an atypical pathogen (including *Legionella pneumophila*), or at the investigators' discretion. In the comparative CAP studies where treatment beyond 7 days was an option, 219/697 (31%) of patients received a duration of treatment beyond 7 days. Because the decision of treatment duration was made on therapy, the results of the 7 day subset cannot be considered as independent of the 14 day subset.

Table 3. FDA Analysis of Clinical Response at Follow up by Duration of Therapy – Clinical Per Protocol Population

7-day CAP studies*	**Treatment Group**	
	Gemifloxacin n/N (%)	**Comparators n/N (%)**
Controlled (011)	102/115 (88.7)	99/113 (87.6)
Uncontrolled (061, 287)	286/315 (90.8)	
Combined (Controlled and Uncontrolled)	388/430 (90.2)	
——— day CAP studies**		
7 days	329/363 (90.6)	319/348 (91.7)
14 days†	200/219 (91.3)	218/237 (92.0)
All patients	529/582 (90.9)	537/585 (91.8)

* includes Studies 011, 061, and 287
** includes Studies 012, 049, and 185 – all were controlled studies
† note: "14-days" includes all patients who were to receive a planned duration of therapy of >7 days.

Bacteriological eradication in the patients who received the 7-day fixed regimen in Studies 011, 061 and 287 are presented below (Table 4)

Table 4. Bacterial Eradication by Pathogen for Patients Treated with Gemifloxacin for 7 Days – From Studies with a Fixed 7-day Duration of Treatment

Pathogen	n/N	%
S. pneumoniae	68/77	88.3
M. pneumoniae	21/22	95.5
H. influenzae	30/35	85.7
K. pneumoniae	11/13	84.6
C. pneumoniae	13/14	92.9
M. catarrhalis	10/10	100.0

The Applicant also evaluated outcomes for patients with CAP by severity based on baseline Fine score. (In most instances, the scoring was applied retrospectively using the available data.) The Applicant initially sought a claim for community acquired pneumonia for gemifloxacin tablets 320 mg po qd for 7 days with no limitation on the severity of disease (i.e., not limited to mild and moderate CAP). The majority of patients enrolled in the CAP studies were Fine category I – III. Approximately 10% of patients enrolled in the CAP studies were categorized as Fine class IV. There were 4 total Fine Class V patients in the ITT population from all of the CAP studies. Analysis of the mortality rates for patients by Fine category in the patients in Fine Class IV were less than what has been reported by Fine et. al.[1] (Table 5).

Table 5. Fine Score Risk Class Specific Mortality Rates - CAP studies/ITT – All Patients

Fine Class (score)*	Data from NDA 21-158 Factive (gemifloxacin)						Data from Fine et. al.[1]			
	Comparative Studies				Non-Comparative Studies		MedisGroups Validation Cohort		Pneumonia PORT Validation Cohort All Patients	
	Gemifloxacin		comparators		gemifloxacin					
	Number of patients	n (%) who died	Number of patients	n (%) who died	Number of patients	n (%) who died	Number of patients	(%) who died	Number of patients	(%) who died
	N	n (%)	n	n (%)	n	n (%)	n	(%)	n	(%)
I	347	1 (0.3%)	369	3 (0.8%)	154	0	3,034	(0.1)	772	(0.1)
II (≤70)	330	2 (0.6%)	287	2 (0.7%)	166	3 (1.8%)	5,778	(0.6)	477	(0.6)
III (71-90)	164	4 (2.4%)	181	3 (1.7%)	63	2 (3.2%)	6,790	(2.8)	326	(0.9)
IV (91-130)	104	5 (4.8%)	90	4 (4.4%)	21	0	13,104	(8.2)	486	(9.3)
V (>130)	4	0	5	1 (20.0%)	0	0	9,333	(29.2)	226	(27.0)
Total	949	12 (1.3%)	932	13 (1.4%)	404	5 (1.2%)	38,039	(10.6)	2287	(5.2)

[1] Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997 Jan 23;336(4):243-50.

Table 7. Bacterial Eradication by Pathogen for Patients Treated in ABECB studies 068, 070, 212 with gemifloxacin 320 mg for 5 days of comparators

Pathogen	Gemifloxacin	Comparators
S. pneumoniae	16/17 (94%)	17/18 (94%)
H. influenzae	32/33 (97%)	30/32 (94%)
H. parainfluenzae	15/15 (100%)	10/11 (91%)
M. catarrhalis	23/25 (92%)	31/31 (100%)

In addition to data in support of safety and efficacy in the treatment of ABECB, the Applicant also provides data regarding other findings from the ABECB studies (e.g., exacerbation free intervals, time to discharge, hospitalizations due to respiratory tract infections, time to eradication of bacterial pathogens, especially *H. influenzae*). These additional findings are considered in the context of the objectives of the study, whether the finding is one of the pre-specified primary or one of several secondary endpoints, whether adjustments have been made for multiple comparisons, and the potential clinical implications of the finding. For the finding of persistence of *H. influenzae*, there was no demonstrated correlation with clinical outcomes. Therefore the clinical relevance of this finding remains unclear.

Safety

Rash

During the review of the initial submission of NDA 21-158 for gemifloxacin a higher than expected rate of rash was noted in the clinical studies. The rates of rash ranged from less than 1% to higher than 25% depending on the age and gender of the population subset being analyzed; patients under 40 years of age and females had a higher incidence of rash. Duration of therapy also correlated with incidence of rash (longer duration therapy was associated with higher rates of rash). Results of rash rates by age, gender, and duration from the original NDA submission (note that the data include a number of indications in addition to ABECB and CAP) are provided in Figure 1.

While a variety of explanations for the lower observed mortality rates in the Fine class IV patients are possible, it is conceivable that the inclusion/exclusion criteria for patients enrolled in a CAP study testing an oral agent led to the enrollment of patients with a more limited spectrum of CAP severity. Hence, a selection bias against including patients with more severe illness may explain the lower mortality rates observed in the Fine class IV patients. There are too few patients of Fine class V to allow any assessments to be made regarding mortality in this group of patients.

The results of the CAP studies showed that the 7-day regimen was noninferior to the comparator, and adequate data were presented for *Streptococcus pneumoniae* (including penicillin-resistant ≥ 2 µg/mL strains), *Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae,* or *Klebsiella pneumoniae.* The label should also reflect that most patients in the clinical studies with *Klebsiella pneumoniae* had CAP of mild or moderate severity.

Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)

The Applicant's proposed labeling and duration for this indication were:

> **Acute bacterial exacerbations of chronic bronchitis** caused by *Streptococcus pneumoniae*; *Haemophilus influenzae*; *Haemophilus parainfluenzae; Moraxella catarrhalis.*

The proposed treatment regimen is 320 mg daily for 5 days.

In the principal ABECB studies submitted to support approval, the results demonstrate that gemifloxacin is non-inferior to its comparator agents (Table 6).

Table 6. Success Rates in the Principal ABECB Studies

Study Number	Success Rate - Clinical PP Population		
	Gemifloxacin* % (n/N)\	Comparator** % (n/N)	Treatment Difference % (95% CI)
068	86.0 (239/278)	84.8 (240/283)	1.2 (-4.7, 7.0)
070	93.6 (247/264)	93.2 (248/266)	0.4 (-3.9, 4.6)
212	88.2 (134/152)	85.1 (126/148)	3.1 (-4.7, 10.7)

* gemifloxacin 320 mg PO once daily for 5 days
** comparators were - study 068: clarithromycin 500 mg bid for 7 days; study 070: amoxicillin/clavulanate 500 mg/125 mg tid for 7 days; and study 212: levofloxacin 500 mg PO for 7 days.

The bacterial eradication rates for the pivotal ABECB studies are presented below (Table 7).

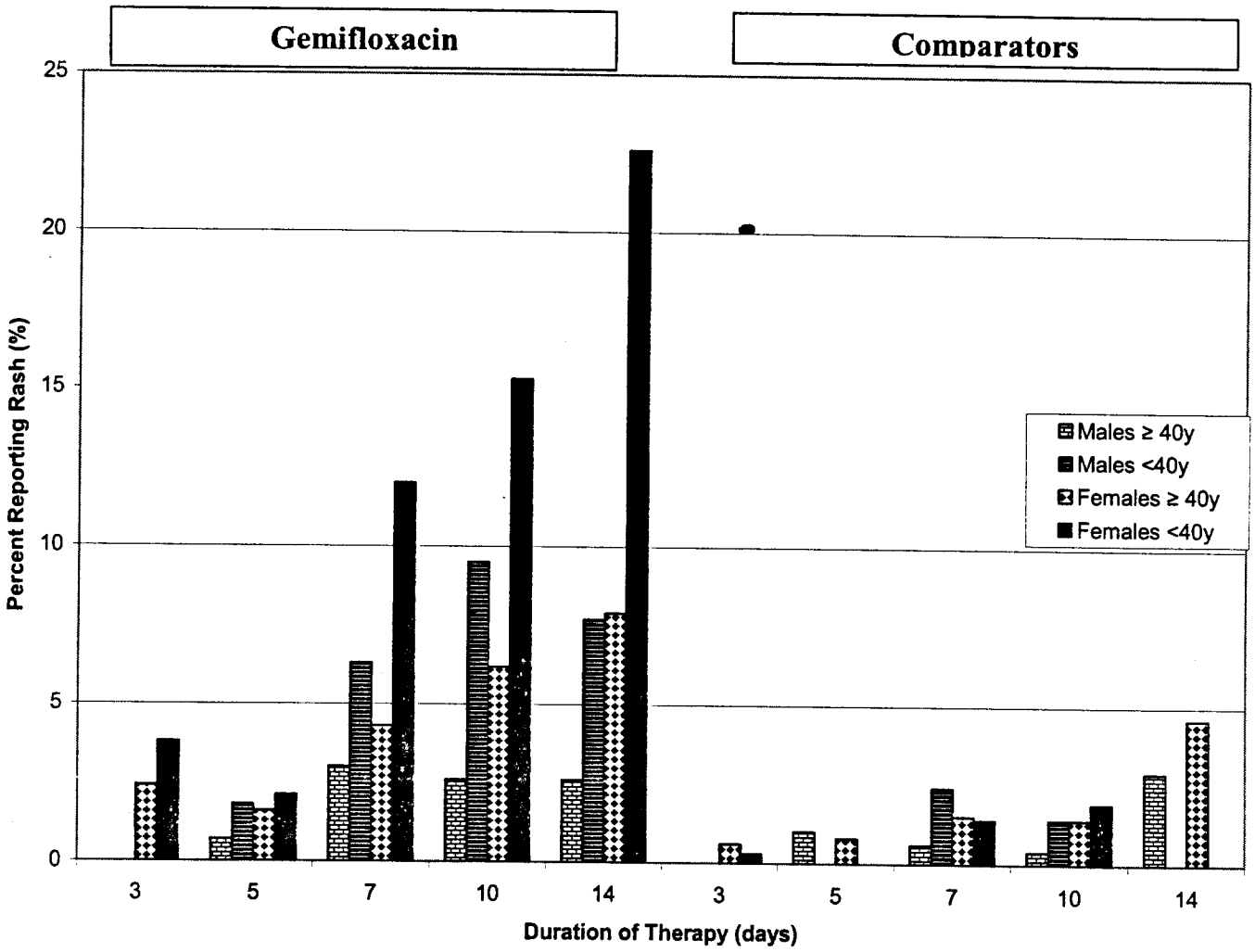

Figure 1. Rates of Rash by Age, Gender, and Duration of Therapy for Gemifloxacin and Comparators – Combined Population – Note includes Data from Phase III Studies from a number of indications. (N.B. Some analysis points are derived from small numbers of patients; See Table 8. Source: Applicant's February 25th, 2003 submission to NDA 21-158.)

The results of the analyses of rates of rash by age, gender, and duration of therapy, from the Phase III studies combined population is also provided in tabular form in order to provide the quantity of observations from which these rates are derived (Table 8).

Table 8. Rates of Rash by Age, Gender, and Duration of Treatment – Gemifloxacin and Comparators – Combined Population

Gender and Age Category	Planned Duration of Therapy									
	3 days		5 days		7 days		10 days		14 days	
	gemi	comps	gemi	comps	gemi	comps	gemi	comps	gemi	comps
Female < 40	10/265 (3.8%)	1/287 (0.3%)	5/242 (2.1%)		39/324 (12.0%)	1/74 (1.4%)	20/131 (15.3%)	6/312 (1.9%)	7/31 (22.6%)	0/24
Female ≥ 40	4/165 (2.4%)	1/157 (0.6%)	19/1210 (1.6%)	1/132 (0.8%)	30/695 (4.3%)	15/1003 (1.5%)	19/308 (6.2%)	9/640 (1.4%)	10/126 (7.9%)	5/108 (4.6%)
Male < 40	0/69		4/218 (1.8%)	0/1	20/318 (6.3%)	2/82 (2.4%)	7/74 (9.5%)	3/211 (1.4%)	3/39 (7.7%)	0/46
Male ≥ 40	0/2		9/1321 (0.7%)	2/201 (1.0%)	23/776 (3.0%)	6/1075 (0.6%)	9/345 (2.6%)	3/756 (0.4%)	3/116 (2.6%)	4/139 (2.9%)
TOTALS	14/501 (2.2%)	2/444 (0.5%)	37/2991 (1.2%)	3/334 (0.9%)	112/2113 (5.3%)	24/2234 (1.1%)	55/858 (6.4%)	21/1919 (1.1%)	23/312 (7.4%)	9/317 (2.8%)

Note includes Data from Phase III Studies from a number of indications.
Source: Applicant's February 25th, 2003 submission to NDA 21-158.

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Because the data in Figure 1 and Table 8 include data from populations beyond just the clinical studies in ABECB and CAP, it provides information about rates of rash in these other populations. This may be an important consideration because the patients outside of a clinical study (i.e., in real world clinical use) may be more heterogeneous than the clinical trials population. For example, based upon data provided by the Applicant regarding antibiotic usage by age and indication, approximately one quarter of antibiotic prescribing for ABECB is for adults between the ages of 19 to 40 years of age.[2] This real world clinical use reflects a patient population that is younger than the clinical trials population. In contrast, in clinical trials of ABECB conducted for this NDA, only 41/2284 (2%) were less than 40 years of age, reflecting more accurately the age groups affected by ABECB, as opposed to acute viral bronchitis.

A study designed specifically to further evaluate gemifloxacin-associated rash was performed (Study 344). The objectives of the study were to characterize the following:

- Clinical and histological characteristics of gemifloxacin-associated rash
- Potential for cross sensitization to ciprofloxacin in subjects who experienced gemifloxacin-associated rash
- Potential for subclinical sensitization to repeat exposure to gemifloxacin in subjects not developing a rash on first exposure to gemifloxacin
- Relationship between plasma levels of gemifloxacin and N-acetyl gemifloxacin and the incidence of rash

Study 344 was a double-blind, double dummy study. Healthy female subjects 18 to 40 years of age were recruited in order to enroll a population at higher risk for gemifloxacin-associated rash. In Part A of the study, subjects were randomized in a 5:1 ratio to gemifloxacin 320 mg po qd or ciprofloxacin 500 mg po bid for 10 days (or until rash developed) (Figure 2). Individuals who developed rash underwent a standardized clinical and dermatological evaluation, skin biopsy, and other standardized laboratory evaluations. Four weeks after completing Part A of the study, subjects entered into Part B of the study. In Part B of the study, subjects who developed rash to gemifloxacin were randomized to receive either placebo or ciprofloxacin 500 mg po bid for 10 days. Subjects that did not develop a rash to gemifloxacin were randomized in a 3:1 ratio to receive either gemifloxacin 320 mg po qd for 10 days or placebo. Subjects who developed a rash to ciprofloxacin received placebo for 10 days in Part B (both "gemifloxacin" and "ciprofloxacin" placebo were received). Patients who did not develop a rash to ciprofloxacin in Part A received ciprofloxacin 500 mg po bid for 10 days.

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[2] Applicant's Briefing Document for NDA 21-158, January 28, 2003, Appendix A, page 152, Table 2.

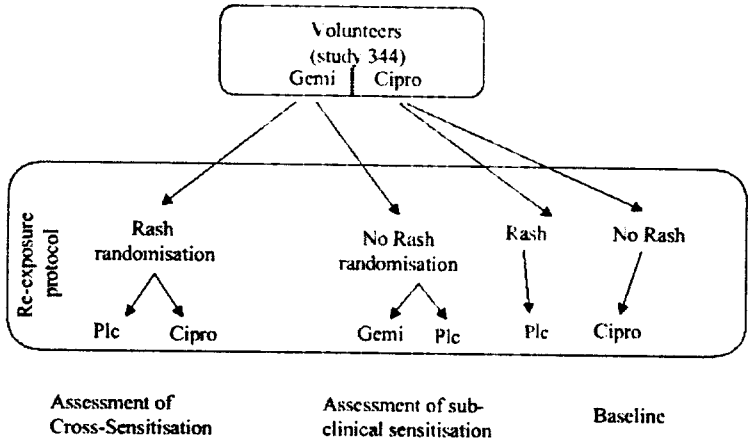

Figure 2. Study Design for Study 344
Source: Applicant's Figure 1, NDA 21-158, Report for Study 344, p. 30

A total of 1011 healthy female subjects enrolled in Part A of Study 344 of which 983 were evaluable. Of these 983 evaluable subjects, 819 received gemifloxacin and 164 received ciprofloxacin. In Part A of the study there were 25 withdrawals due to rash-related AEs, all were in the gemifloxacin arm of the study. This represents approximately 3% of the patients in the gemifloxacin arm in Part A. (Note: more patients were enrolled in the gemifloxacin arm in Part A because of 5:1 randomization.)

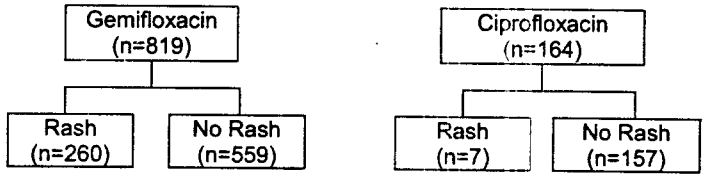

Figure 3. Summary of subject disposition in Part A
Source: Applicant's Figure 1, NDA 21-158, Report for Study 344, p. 88

In the gemifloxacin arm in Part A, 31.7% (260/819) of subjects developed rash. The rate of rash in the ciprofloxacin arm was 4.3% (7/164) (Table 9).

Table 9. Point Estimates and 95% Confidence Intervals for Incidence of Rash in Part A

Regimen	No. of Subjects	Subjects With Rash	Point Estimate (%)	95% C.I. Normal Approximation	Exact Method
Gemifloxacin	819	260	31.7	(28.5, 35.0)	(28.6, 35.1)
Ciprofloxacin	164	7	4.3	(0.9, 7.7)	(1.7, 8.6)

Source: Applicant's Table 14.1 from NDA 21-158 18 month Safety Update

In Part A, the median day of onset of gemifloxacin associated rash was day 9 and the median number of days of duration of gemifloxacin-associated rash was 6 days.

The clinical descriptions of the rashes experienced in Part A by treatment group are summarized in Table 10. The most frequently reported rash findings/symptoms were macules, papules, and pruritus.

Table 10. Summary of Description of Rash in Part A by Regimen and Severity.

Regimen	Severity			
Description	Mild (%)	Moderate (%)	Severe (%)	Total (%)
Gemi (n=260)	161/260 (62)	80/260 (31)	19/260 (7)	260/260 (100)
Macules	125 (48.1)	70 (26.9)	14 (5.4)	209 (80.4)
Papules	122 (46.9)	71 (27.3)	17 (6.5)	210 (80.8)
Plaques	15 (5.8)	11 (4.2)	3 (1.2)	29 (11.2)
Pruritus	99 (38.1)	65 (25)	16 (6.2)	180 (69.2)
Skin Tenderness	12 (4.6)	6 (2.3)	4 (1.5)	22 (8.5)
Urticaria	18 (6.9)	6 (2.3)	6 (2.3)	30 (11.5)
Cipro(n=7)	6/7 (85.7)	1/7 (14.3)	0 (0)	7/7 (100)
Macules	3 (42.9)	0 (0)	0 (0)	3 (42.9)
Papules	5 (71.4)	1 (14.3)	0 (0)	6 (85.7)
Pruritus	3 (42.9)	1 (14.3)	0 (0)	4 (57.1)

Source: Applicant's Table 14.5 fromNDA21-158 Report of Study 344 Appendix C

In Part A of the study there was a greater proportion of patients in the gemifloxacin group with larger proportions of surface area scored as covered with rash (Table 11).

Table 11. Summary of Surface Area Covered with Rash by Regimen and Severity of Rash in Part A

	Surface Area	Severity			
Regimen	Covered	Mild	Moderate	Severe	Total
Gemifloxacin	Unknown	5 (1.9%)	0 (0.0%)	0 (0.0%)	5 (1.9%)
	0 - 5%	37 (14.2%)	3 (1.2%)	0 (0.0%)	40 (15.4%)
	6 - 10%	21 (8.1%)	4 (1.5%)	2 (0.8%)	27 (10.4%)
	11 - 20%	32 (12.3%)	7 (2.7%)	0 (0.0%)	39 (15.0%)
	21 - 40%	21 (8.1%)	12 (4.6%)	2 (0.8%)	35 (13.5%)
	41 - 60%	28 (10.8%)	17 (6.5%)	2 (0.8%)	47 (18.1%)
	>60%	17 (6.5%)	37 (14.2%)	13 (5.0%)	67 (25.8%)
	Total	**161 (61.9%)**	**80 (30.8%)**	**19 (7.3%)**	**260 (100.0%)**
Ciprofloxacin	Unknown	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	0 - 5%	4 (57.1%)	0 (0.0%)	0 (0.0%)	4 (57.1%)
	6 - 10%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	11 - 20%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	21 - 40%	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	41 - 60%	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
	>60%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	**6 (85.7%)**	**1 (14.3%)**	**0 (0.0%)**	**7 (100.0%)**

Source: Applicant's Table 14.6 from NDA 21-158 Report of Study 344 Appendix C

There were 16 subjects for whom mucus membrane involvement was noted among the 260 subjects who developed gemifloxacin rash (6.2%) and none in

the 7 subjects who developed a rash secondary to ciprofloxacin. Review of the available case report forms revealed 5 subjects with one to a few ulcerations, erosions, papules, or vesicles inside the mouth or on the lips; 2 patients had erythema of the lips or inside the mouth, one of whom received systemic steroids; 2 additional subjects had illegible descriptions of the oral findings on the case report forms, one of whom received systemic steroids.

Patient disposition in Part B of Study 344 is summarized in Figure 4.

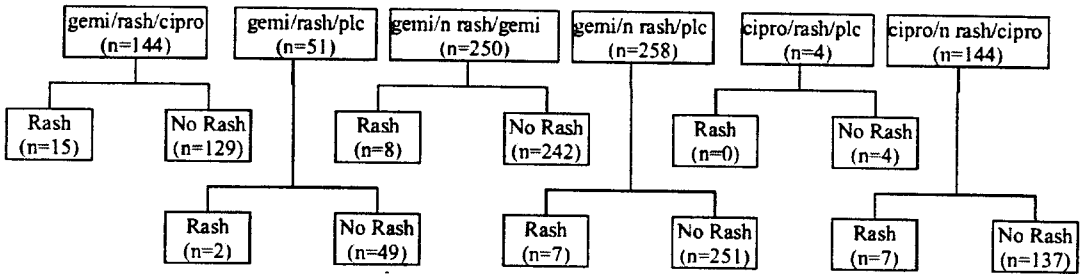

Figure 4. Patient Disposition in Part B of Study 344

The rates of rash for the Part B subjects in the Gemi/rash/cipro group was 5.9% compared to 2.0% in the Gemi/rash/placebo group (Table 12). As noted previously, one of the objectives of the study was to make an assessment of the degree of cross-sensitization of gemifloxacin to ciprofloxacin.

Table 12. Point Estimates and 95% Confidence Interval for Incidence of Rash in Part B – Excludes Center 027*

Regimen	No. of Subjects	Subjects with Rash	Point Estimate (%)	95% C.I. Normal Approximation	Exact Method
Gemi/rash/cipro	136	8	5.9	(1.6, 10.2)	(2.6, 11.3)
Gemi/rash/plc	50	1	2.0	(0.0, 6.9)	(0.1, 10.6)
Gemi/N rash/gemi	248	6	2.4	(0.3, 4.5)	(0.9, 5.2)
Gemi/N rash/plc	256	5	2.0	(0.1, 3.8)	(0.6, 4.5)
Cipro/rash/plc	4	0	0.0	(0.0, 12.5)	(0.0, 60.2)
Cipro/N rash/cipro	141	5	3.5	(0.1, 7.0)	(1.2, 8.1)

Data Source: Applicant's Table 21 NDA 21-158, Study Report Study 344, p. 00093.
*Excluded because of a remarkably high rate of rash and lack of corroborative evidence to support the high rash rate in Part B (e.g., photographs confirming the presence of rash)

Skin biopsies for histopathologic evaluation were obtained from 288 of the 299 total rash episodes in Parts A and B of Study 344 secondary to gemifloxacin,

ciprofloxacin, or occurring in the placebo arm. Punch biopsies were obtained from both affected and unaffected skin. Specimens were evaluated by routine histologic examination, immunophenotypic evaluation, and stained for immunoflourescence for IgG, IgM, IgA, and C3.

The following findings were obtained:

- Most common finding-mild superficial perivascular infiltrate
- 10 cases of moderate superficial or deep perivascular infiltrate
- 10 cases of eosinophils in the infiltrate (1 in unaffected skin)
- T cell type infiltrate, both CD-4 and CD-8 with no common pattern noted
- No evidence of vasculitis
- Activation of endothelial cells –staining for ICAM and HLA-DR
- HLA-DR staining was noted in a significant number of cases
- Immunoflourescence revealed faint deposits of IgM and/or C3 in dermal vessels "lumina" in some cases of unaffected and affected skin
- One case of linear IgM along basement membrane (affected and unaffected skin)
- No bulla formation, no epidermal or eccrine necrosis

In clinical studies of ABECB and CAP, the incidence of rash by age and gender at the proposed treatment duration is presented in the table below (Table 13).

Table 13. Incidence of Rash by Age and Gender at the Proposed Treatment Duration, Clinical Studies of ABECB and CAP

	ABECB (5 days) N = 2284		CAP (7 days) N = 643	
	n/N	%	n/N	%
Totals	27/2284	1.2	26/643	4.0
Females, < 40 years	*		8/88	9.1
Females, ≥ 40 years	16/1040	1.5	5/214	2.3
Males, < 40 years	*		5/101	5.0
Males, ≥ 40 years	11/1203	0.9	8/240	3.3

* only 22 females under 40 and 19 males under 40 years were enrolled in the ABECB trials

Liver

In addition to gemifloxacin-associated rash, there have also been questions regarding the hepatic safety of gemifloxacin. In preclinical studies in dogs, gemifloxacin was associated with cholangitis and pericholangitis associated with hepatocellular degeneration and single cell necrosis. Also noted was crystalline material that had deposited in the bile ducts and bile canaliculi. Spectroscopic

analysis found the deposited material to be gemifloxacin or gemifloxacin-derived material. In studies in women who received a single dose of 640 mg (twice the proposed dose of 320 mg) there was a greater proportion of patients that developed elevations of AST and ALT at the On-therapy visit compared to women receiving a ciprofloxacin comparator. (Results for ALT are shown in Table 14.)

Table 14. Number (%) of Patients with ALT Values in the Specified Ranges at the On-Therapy Visit (Gemifloxacin 640mg vs. Ciprofloxacin 250mg, Patients In-Range at Screening)

Analyte	Range	Treatment Group: Gemifloxacin 640mg Single Dose N =638		Ciprofloxacin 250mg bid N = 662	
		n/N*	(%)	n/N*	(%)
ALT	<ULN	569/592	(96.1)	600/606	(99.0)
	ULN-<2xULN	14/592	(2.4)	6/606	(1.0)
	2-<4xULN	4/592	(0.7)	0/606	
	4-<6xULN	1/592	(0.2)	0/606	
	6-<8xULN	3/592	(0.5)	0/606	
	≥8xULN	1/592	(0.2)	0/606	

Data Source: Applicant Table 370 from NDA 21-158 ISS
*n/N= number of patients outside limit/number of patients evaluated for the particular parameter

In the clinical studies in the combined population, the proportion and levels of elevations of ALT and AST were similar between treatment groups. With regards to serious adverse events, there were three patients within the gemifloxacin treated patient group with the adverse event of hepatic enzymes increased. Review of these cases and other selected patients with hepatic adverse events suggested the possibility that gemifloxacin may induce elevated hepatic enzymes and raises the question whether this is a signal for the potential for more serious less frequent adverse events involving the liver. The hepatic safety profile was one of the issues discussed by the Anti Infective Drugs Advisory Committee (supplemented with expert hepatologists). (The reader is referred to the Advisory Committee Comments and Recommendations section of this review.)

Cardiac Repolarization

Gemifloxacin, similar to some of the other members of the quinolone class, appears to have the capacity to effect cardiac repolarization. In the NDA clinical studies in the combined population, gemifloxacin was associated with a mean degree of QT prolongation of $\leq$ 5 milliseconds.

Advisory Committee Comments and Recommendations:

The Factive (gemifloxacin) application was presented before the Anti Infective Drugs Advisory Committee on March 4, 2003 at the Washingtonian Marriott in Gaithersburg, Maryland. Following presentations by Dr. Michael Bigby (dermatology consultant), the company, and the agency, the committee was asked to discuss and vote on the following questions:

QUESTION 1.
Based on the data presented and in your scientific and clinical opinion, do the benefits of gemifloxacin therapy outweigh the risks for the proposed indications of?

(a) Community acquired pneumonia
(b) Acute bacterial exacerbation of chronic bronchitis

Please include as part of your discussion:

- the clinical and microbiologic benefits of gemifloxacin
- the significance of the rash, particularly as it relates to the likelihood of more severe dermatological manifestations with broader use and the likelihood of cross-sensitization to other fluoroquinolones
- The hepatic toxicity profile of the drug

Nineteen voting members and SGE's were present and all 18 recommended approval of mild-moderate CAP while 15 recommended ABECB approval.

The group also recommended that approval be given for *Streptococcus pneumoniae* including strains that are resistant to penicillin; during the meeting Dr. John Powers gave a presentation on the in-vitro finding of multi-drug resistance among *S. pneumoniae*, including penicillin, macrolides, 2nd generation cephalosporins, tetracycline and trimethoprim/sulfa. He proposed that the organism be referred to as "multi-drug resistant *S. pneumoniae*" in lieu of "penicillin-resistant *S. pneumoniae*" to help educate clinicians and others about the issue.

The dermatology consultants commented that the rash described with gemifloxacin was characteristic of a drug exanthematous reaction and did not portend or preface a more serious reaction such as SJS or TEN.

The hepatologist consultants commented that the data characterizing the hepatic safety profile (preclinical through clinical data) did not portend a risk for more serious infrequent hepatocellular injury. The abnormalities noted were thought to most consistent with a cholestatic pattern and therefore not likely to be associated with more severe hepatocellular injury.

QUESTION 2.
If the answer to question (1a/1b) is yes, please discuss the types of information that should be provided to physicians and patients. Please focus on the

elements outlined in question 1 as well as any other issues you believe relevant. Please include as part of this discussion any caveats as to how and to whom the drug should be administered. For any risk communication/management strategy that may be appropriate, please comment on how practical and/or effective such strategies may be.

Members of the committee and consultants suggested the package insert provide factual information describing the rash seen in clinical studies and identify the population subsets including young patients and women who are most likely to develop the rash. Additional advice from the committee on the issue of rash was that the label should not be prescriptive regarding patient management, but that stating the facts should provide the information that healthcare providers need to make clinical decisions. Some of the dermatologists stated they might treat through a drug-related exanthematous rash and suggested a patient did not need to stop in all cases. There were also comments from some members of the committee that a patient who developed a rash to gemifloxacin should not generally be rechallenged or receive a drug in the fluoroquinolone class. As part of risk management, suggestions including providing education materials, limiting recommended duration of therapy to 7 days or shorter, recommending no refills.

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QUESTION 3.
If the answer to (1a/1b) is no, please recommend what additional studies or information should be obtained for

(a) Community acquired pneumonia
(b) Acute bacterial exacerbation of chronic bronchitis

The committee suggested further questions to be addressed include: rash and risk with other quinolones; additional data on the effects of rash in patients of color; activity against resistant organisms; placebo-controlled trials in ABECB.

Post Marketing Studies / Risk Management Evaluation:

DSPIDP requested consults from the Office of Drug Safety and received reviews of the company's proposed risk management plan from the Division of Drug Risk Evaluation (DDRE) and the Division of Medication Errors and Technical Support (DMETS) as well as a review of the proposed Patient Package Insert from the Division of Surveillance, Research, and Communication Support (DSRCS). DSPIDP participated in a preapproval safety conference with ODS on March 19, 2003.

Based on the advice from these consults, DSPIDP asked the company to revise the Patient Package Insert and the cartons for gemifloxacin unit dose packs and

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to agree to the following Phase 4 studies to better evaluate the risk management plans for gemifloxacin.

Following discussion with the Division, the Applicant agreed to conduct the following post-approval studies (see letter dated March 28, 2003) safety profile of the product in actual use studies as well as evaluate the risk management plan by assessing the prescribing patterns of gemifloxacin and examining the spontaneous adverse reactions reported after approval.

Phase 4 Study

LG Life Sciences will conduct a phase 4 safety study of gemifloxacin. The design will be a prospective, randomized, active control trial. Randomization will be at a ratio of two gemifloxacin patients (n=5,000) to one active control patient (n=2,500). Inclusion criteria will include the presence of community acquired pneumonia (CAP) or acute bacterial exacerbation of chronic bronchitis (ABECB). In addition, LG Life Sciences will strive to ensure that the patient population enrolled consists of at least 10% of the following ethnic minorities: people of African origin, Asian origin and Hispanic origin so as to achieve a better understanding of the clinical course – specifically as relates to rash – of these patient populations. CAP patients will be treated for seven days; ABECB patients will be treated for five days. Patients will be monitored for efficacy and safety. Safety evaluations will include monitoring for adverse events – with particular emphasis on rash – as well as monitoring for laboratory abnormalities: liver function tests, CPK, and ECG in patients at risk for cardiac arrhythmias.

There will be annual interim analyses of the data from this trial. The timing of the interim analyses will be such as to allow for their results to be included in gemifloxacin Annual Reports to the FDA.

LG Life Sciences commits to forward to the FDA, within two months of NDA approval for gemifloxacin, a draft Phase 4 protocol for this trial and to incorporate changes requested by the FDA and agreed with LG Life Sciences within one month of their finalization. LG Life Sciences commits to initiate the study by the winter of 2004 and to complete the study within three to four years.

Prescribing Patterns and Use

LG Life Sciences commits to obtaining data on the prescribing patterns and use of gemifloxacin. These data will include the number of prescriptions issued as well as the rate of refills. To obtain these data, LG Life Sciences will utilize various databases from HMOs, governmental agencies, and pharmacy organizations. These data will be submitted in the gemifloxacin NDA Annual Reports and will be utilized to estimate not only the quantity of gemifloxacin being utilized, but also the appropriateness – as defined by the gemifloxacin label – of the prescribing patterns.

Evaluation of Spontaneous Adverse Event Reports

LG Life Sciences commits to including in the NDA Annual Reports enhanced sections on adverse events related to the following organ systems: hepatic, skeletal muscle, cardiac conducting system, and cutaneous. For each of these organ systems, spontaneous adverse events will not only be categorized and quantified, but there will also be an effort made to estimate the rates of these adverse events by estimating the rate of underreporting of these events and the amount of patient exposure. In addition, results from the interim analyses of the Phase 4 study will be incorporated into the appropriate

sections of the Annual Report related to these four organ systems. These analyses will thus allow for a reanalysis of the risk/benefit ratio of gemifloxacin and will enhance the ability to discern a safety signal related to one or more of these organ systems.

Case Control Studies

If a safety signal is identified for a rare but serious toxicity – especially severe hepatotoxicity, torsades des pointes, TENS or Steven Johnson Syndrome, or rhabdomyolysis – LG Life Sciences commits to conducting a retrospective case control study. The goal of such a study will be to estimate the relative risk for this toxicity occurring among patients receiving gemifloxacin compared to other therapies. For this case control study, LG Life Sciences will utilize readily available patient databases, such as are available through various HMOs or governmental agencies. The case control protocol will be developed using standard accepted principles and will be sent for FDA review and input prior to initiation.

Summary Recommendations

The data provided in the original submission to NDA 21-158 as well as the additional data provided in the resubmission provide evidence of gemifloxacin's efficacy and safety and support a satisfactory risk benefit ratio for the use of Factive (gemifloxacin) for the treatment of the following indications:

- Community acquired pneumonia (CAP) of mild to moderate severity caused by *Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin ≥2µg/mL), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *Klebsiella pneumoniae*.
- Acute bacterial exacerbation of chronic bronchitis (ABECB) caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Moraxella catarrhalis*.

Integral to the risk-benefit calculus that supports a satisfactory risk-benefit ratio for Factive (gemifloxacin) is providing information to the prescriber that describes gemifloxacin-associated rash and the risk factors for rash [female gender, young adults (i.e., <40 years of age), longer duration of therapy (i.e., >7 days), and hormone replacement therapy in women.] With this information prescribers and their patients will be in a position to best make an informed decision regarding Factive (gemifloxacin) therapy. In accordance with advice provided by the Anti Infective Drugs Advisory Committee, we will focus on providing information in the label that describes gemifloxacin-associated rash and will not be overly prescriptive in directing physicians regarding counteractive measures in the setting of rash. In an effort to reduce prescribing beyond the recommended duration, 5- or 7-day unit dose packs will be the presentations available through outpatient pharmacies.

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ON ORIGINAL

Post Approval Issues

- [redacted]
- [redacted]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Cox
4/4/03 01:25:47 PM
MEDICAL OFFICER

Renata Albrecht
4/4/03 03:39:07 PM
MEDICAL OFFICER

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NDA 21-158

FACTIVE® (gemifloxacin mesylate) 320mg Tablets

Action Date: December 15, 2000

TL: Leissa

MO: Powers, Alivisatos, Cox

CHM: M. Sloan

PCL: Ellis

MIC: Dionne

BPH: Colangelo

STT: Higgins, Dixon, Silliman

RPM: Kimzey

SB
SmithKline Beecham
Pharmaceuticals

FACSIMILE

To: Ms. Rene Kimzey
(301) 827-2326

From: Mr. Thomas Hogan
Telephone (610) 917-6605
Fax (610) 917-4704

Date: 24 January 2000

Page 1 of: 1

Message:

RE: Establishment Evaluation Request Summary (EES) - NDA 21-158
Factive (gemifloxacin mesylate) 320 mg Tablets

Ms Kimzey:

Per your request on Friday, January 21, 2000, please accept this facsimile as a confirmation that the facilities listed in the EES (LG Chemical) ______________________ are ready for inspection with regard to NDA 21-158 for Factive (gemifloxacin mesylate) 320 mg tablets.

Also, I will serve as the point of contact should inspections of any of the aforementioned facilities need to be scheduled.

Should you require any additional information, please do not hesitate to contact me by telephone at (610) 917-6605 or by fax at (610) 917-4704.

Sincerely,

Thomas M. Hogan
Director,
North America Regulatory Affairs

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989
Telephone (610) 917 7000 Fax (610) 917 7707

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21158/000
Stamp: 16-DEC-1999
Regulatory Due: 16-OCT-2000
Applicant: SKB PHARMS
1 FRANKLIN PLAZA
PHILADELPHIA, PA 191017929
Priority: 1S
Org Code: 590

Action Goal:
District Goal: 17-AUG-2000
Brand Name: FACTIVE(GEMIFLOXACIN MESYLATE)320MG TAB
Estab. Name:
Generic Name: GEMIFLOXACIN MESYLATE

Dosage Form: (TABLET)
Strength: 320 MG

Application Comment:
FDA Contacts: L. KIMZEY (HFD-590) 301-827-2196 , Project Manager
M. SLOAN (HFD-520) 301-827-2182 , Review Chemist
N. SCHMUFF (HFD-590) 301-827-2425 , Team Leader

Overall Recommendation:

Establishment:
LG CHEMICAL LTD
599 YONGJEI-DONG
IKSAN CITY, CHUNBUK-DO, KS 570-350

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DMF No: ——— AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: CSN OAI Status: NONE
Estab. Comment: READY FOR PAI (on 06-JAN-2000 by M. SLOAN (HFD-520) 301-827-2182)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-JAN-2000				SLOANM

Profile: CTL OAI Status: NONE
Estab. Comment: READY FOR PAI (on 06-JAN-2000 by M. SLOAN (HFD-520) 301-827-2182)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-JAN-2000				SLOANM

Establishment: 2650232
SB PHARMCO PUERTO RICO INC
RD 172 KM 9.1 BO CERTENEJAS
CIDRA, PR 007391975

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DMF No: ——— AADA:
Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER

Profile: CTL OAI Status: NONE
Estab. Comment: FACILITY READY FOR PAI (on 04-JAN-2000 by M. SLOAN (HFD-520) 301-827-2182)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-JAN-2000				SLOANM

Profile: TCM OAI Status: NONE
Estab. Comment: FACILITY READY FOR PAI (on 04-JAN-2000 by M. SLOAN (HFD-520) 301-827-2182)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-JAN-2000				SLOANM

Establishment: 9614352
SMITHKLINE BEECHAM PHARMACEUTICALS

THIRD AVENUE
HARLOW, ESSEX, UK CM19 5AW

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: FACILITY READY FOR PAI (on 04-JAN-2000 by M. SLOAN (HFD-520) 301-827-2182)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-JAN-2000				SLOANM

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Please See Dr. John Powers's Safety Review under Clinical Reviews Section (Book 3)

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PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-158 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: October 4, 2002 Action Date: April 4, 2003

HFD 590 Trade and generic names/dosage form: Factive® (gemifloxacin mesylate) 320mg Tablets

Applicant: LG Life Sciences Therapeutic Class: 4030100

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Acute Bacterial Exacerbation of Chronic Bronchitis

APPEARS THIS WAY ON ORIGINAL

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
X Too few children with disease to study
☐ There are safety concerns
☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other: _____

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If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for deferral:

APPEARS THIS WAY ON ORIGINAL

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appened electronic signature page}

APPEARS THIS WAY ON ORIGINAL

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Community-Acquired Pneumonia of mild to moderate severity

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- X **No: Please check all that apply: ____Partial Waiver __X__Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr.____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.